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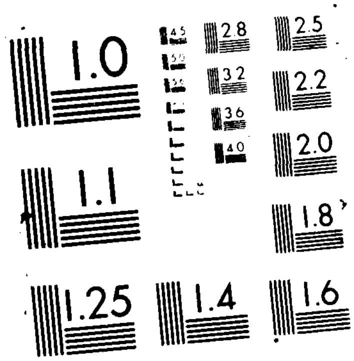
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MANUSCRIPT: Dexamethasone and AMS

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DEXAMETHASONE AS PROPHYLAXIS FOR ACUTE MOUNTAIN SICKNESS: EFFECT OF DOSE LEVEL

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ABSTRACT

Rapid exposure of unacclimatized individuals to high altitude causes a syndrome termed acute mountain sickness (AMS). Prophylactic treatment with high doses of dexamethasone is known to prevent AMS, but carries a high risk of side effects. To determine whether lower doses with less potential for side effects were effective in preventing AMS, 28 men between the ages of 18 and 32 were exposed to a simulated altitude of 4579 m for 45 h in a hypobaric chamber on two occasions while taking one of three doses of dexamethasone (4 mg, 1 mg or .25 mg every twelve hours) or a placebo in a double-blind, crossover design. Three independent measures for the presence of AMS showed that the 4 mg dose of dexamethasone reduced the incidence of AMS symptoms compared to placebo and compared to the other dose levels. Dexamethasone did not alter fluid balance or plasma volume changes, but treatment with 1 mg and 4 mg suppressed cortisol secretion. There was no evidence of adrenal cortical suppression after treatment with dexamethasone or placebo 48 h after discontinuing altitude exposure and drug treatment. The results indicate that doses of dexamethasone less than 4 mg twice daily may not be effective prophylactic treatment for AMS.

INTRODUCTION

Acute mountain sickness (AMS) is a syndrome induced by hypoxia in unacclimatized individuals who ascend rapidly to high altitude and remain there for more than several hours. Characteristic symptoms include headache, nausea, vomiting, anorexia, lassitude and sleep disturbances. The onset occurs three to twelve hours after an ascent, and symptoms usually remit gradually over three to seven days as acclimatization occurs. The severity of symptoms is directly related to altitude (ie. the degree of hypoxia), the rate of ascent and probably also to individual differences in ability to acclimate to hypoxia. While the pathophysiology of AMS has never been clearly demonstrated, most researchers feel the symptoms are due to hypoxia-induced subclinical cerebral edema (Hansen and Evans, 1970; Houston and Dickson, 1975; Sutton and Lassen, 1979).

As mountain recreation has increased in popularity over the past several decades and improvements in transportation have made the high mountains increasingly accessable, more and more people have suffered AMS. This increased frequency of AMS has generated interest in prophylactic measures. Staging, gradual ascent with frequent 1-2 day halts to allow acclimatization, may be the most successful means of preventing AMS (Robinson et al., 1974; Hackett and Rennie, 1978), but this strategy is not always practical for individuals with a limited amount of recreation time. Prophylaxis with pharmacologic agents offers an alternative to staging, but until recently, the only drug accepted for this purpose was acetazolamide, which is only partially effective in controlling symptoms (Forwand, et al., 1968) and has undesirable side effects.

In a double-blind crossover trial reported in 1984, Johnson et al. demonstrated that prophylaxis with 4 mg dexamethasone every 6 h was highly effective in preventing

AMS symptoms in healthy young men rapidly exposed to 4570 m altitude in a hypobaric chamber. A subsequent study using the same dose regimen at 4300 m on the summit of Pikes Peak, Colorado showed similar results (Rock et al., in press), although subjects taking dexamethasone showed symptoms of AMS when the drug was discontinued.

While the two studies cited above suggest that dexamethasone may be potentially useful in preventing AMS, the high dose (16 mg/day) of this powerful corticosteroid carries the potential of inducing significant morbidity. Although the incidence of side effects noted in the chamber study was low (Johnson et al, 1984), a significant number of side effects was noted in the study on Pikes Peak (Rock, unpublished data). Further, the symptoms experienced by subjects after discontinuing the drug during that study could be interpreted as resulting from steroid withdrawal (Rock et al., in press). A lower dose of dexamethasone would decrease the frequency of side effects and steroid withdrawal, but might not be effective in preventing AMS.

In the present study, we examined the value of three dose regimens of dexamethasone less than 16 mg/day to determine if they were effective in preventing AMS in young men acutely exposed to 4572 m simulated altitude in a hypobaric chamber. The results suggest that a regimen using a dose of 4 mg of dexamethasone twice a day is effective in reducing AMS symptoms, but lower doses are not.

MATERIAL AND METHODS

Twenty-eight young, healthy men served as test subjects after giving their informed consent. All were life-long residents at low altitude, and none had experienced any prolonged exposure to altitudes greater than 2500 m in the six months immediately preceeding the study. Each subject underwent a review of his medical history, a physical examination and laboratory screening prior to inclusion in the study. Potential subjects with any contraindication to taking dexamethasone or to undergoing altitude exposure were excluded from participation in the study. The mean (±S.D.) age, height and weight of the subjects was 22.3±2.4 yrs, 178.1±7.7 cm and 79.6±12.3 kg, respectively.

A double-blind, placebo-controlled, crossover design was used in which each subject served as his own control. Prior to the beginning of testing, 30 subjects were assigned at random by an individual not involved in the data collection to a dose regimen of either 0.25 mg, 1 mg or 4 mg dexamethasone orally every twelve hours. Two assigned subjects were unable to participate for personal reasons and withdrew from the study prior to the beginning of testing. The remaining subjects were exposed to a simulated altitude of 4590 m (428 torr) for 45 hours in a hypobaric chamber on two occasions separated by three weeks. On one exposure they were given their assigned dose regimen of dexamethasone and on the other an identically appearing placebo containing lactose. The order of treatment was randomly assigned to each subject, but was counterbalanced for the total number of subjects in each group to minimize any order effects. Neither the subjects nor the investigators collecting the data were aware of which treatment the subjects were receiving during drug administration and data collection.

Four of the 28 subjects who participated in the first altitude exposure did not participate in the crossover phase of the study. Two were excluded due to viral illness, and two were withdrawn for administrative reasons unconnected with the study conditions. The data from these four individuals were not included in the analysis.

Subjects were exposed to altitude in groups of four or five containing individuals from each dose regimen. They entered the altitude chamber at 1500 h on the day prior to ascent to participate in sea level testing. At 0700 h the next morning they received their first dose of medication. At 1900 h that same day they received a second dose and the chamber was evacuated to the simulated altitude of 4590 m (428 torr) at a rate of 600 m/min. The subjects remained at that altitude for 45 h. While in the chamber, they were given unrestricted access to a nutritionally balanced diet and were free to pursue sedentary leisure activities when not involved in testing. They continued to take dexamethasone or placebo at 0700 h and 1900 h throughout the altitude exposure.

Subjective symptoms of AMS were assessed twice daily at sea level and at altitude using the Environmental Symptoms Questionnaire (ESQ) and a physician's clinical interview. The ESQ is a 67-question inventory of symptoms which occur in stressful environments including heat, cold, and high terrestrial altitude (Sampson and Kobrick, 1980). It was administered to the subjects individually using an interactive computer software package (Fulco et al., 1985). The program queried each subject about specific symptoms, and he then chose one of six phrases ranging from "not at all" to "extreme" to quantify the presence and severity of that symptom within himself at that moment. The responses were assigned values from 0 (not at all) to 5 (extreme), and a weighted average of cerebral symptoms termed "AMS-C" and respiratory symptoms termed "AMS-R" were derived from the scores. These measures have been shown in previous studies to accurately and reliably identify individuals suffering AMS (Sampson et al., 1983).

The clinical interview was performed by a physician (RFL) who was unaware of the subject's responses on the ESQ at the time of the interview. He examined the subjects for rales and peripheral edema and recorded the presence of specific altitude related symptoms such as headache, nausea, dyspnea and sleep disturbances. Following the completion of the study, symptom scores were calculated for each subject on the basis of a scale reported by Johnson et al. (1984) as follows: 0-no symptoms; 1-mild headache or nausea; 2-moderate headache and nausea; and 3-severe headache, nausea and vomiting, or some combination of these. A score of 1 or greater was considered to be indicative of AMS.

To obtain an additional perspective of each subject's overall state of well being during the intervals between symptom assessments, the subjects were asked to rate each other. Twice daily at sea level and altitude, each test subject was given a list of the names of the other subjects in the group and was asked to rate those subjects as "well, sick" or "very sick." Each was instructed to make his assessment on the basis of what he had observed of his companions during the preceeding 12 h and was not allowed to query them about their condition. The ratings were scored as 0-well, 1-sick and 2-very sick. A mean score for each subject was calculated for each rating period.

Because the pathophysiology of AMS may involve changes in body fluid balance and a previous study suggested a correlation between AMS scores and changes in urine output (Johnson et al., 1984), several measures indicative of fluid status were obtained. All fluid and food intake and the volume of urine output were recorded. Blood samples were taken without stasis from a peripheral arm vein every morning before the subjects arose for determination of hemoglobin (Hb) and hematocrit (Hct), and plasma volume changes were calculated from these values using the method of Strauss et al. (1951). Nude body weights were measured daily after the first morning urine voiding.

The effect of dexamethasone on the adrenal cortex was assessed by measuring plasma cortisol levels twice daily while the subjects were taking dexamethasone or placebo. The first blood sample for cortisol determination was taken at 0800 h. prior to the subjects' arising. The second daily sample was taken at 1600 h. after the subjects had been upright in a seated or standing position for at least one hour.

An ACTH stimulation test was given to each subject 48 h after returning to sea level following each exposure to determine if the drug regimen had caused any degree of adrenal supression. During this test, subjects were at rest in a seated position. A catheter was inserted into a peripheral vein in the forearm and a sample was taken for cortisol analysis. Each subject was then injected with .25 mg cortrosyn (Organon Pharmaceuticals, West Orange, NJ) into the deltoid muscle of the shoulder. Repeat blood samples were taken at 30 min and 60 min for cortisol analysis. Plasma cortisol levels were determined using commercially available RIA kits (Diagnostic Products Corporation, Los Angeles, CA).

Statistics

Values are represented as mean±S.E.M. except where noted. The ESQ, fluid status and hormonal data were analyzed with a two-way ANOVA for repeated measures using BMDP software on a VAX 11/780 computer (Digital Equipment Corp.; Maynard, MA). Significant differences were localized by post hoc testing using Tukey's method (Bruning and Kintz, 1977). Data from the clinical interview and peer review were analyzed with a Wilcoxon signed rank test using BMDP software on the VAX 11/780 computer to compare paired differences between dexamethasone and placebo treatments. All tests were two-tailed, and the level of significance was considered to be $p \leq .05$.

RESULTS

Dexamethasone had no discernable effect on any of the symptom scores at sea level. There were no statistically significant differences between mean scores on dexamethasone and placebo for any of the doses, and there were no significant differences between doses.

The pattern of ESQ symptom scores while taking placebo during altitude exposure (Table 1) was similar to that which has been previously observed in other chamber studies (Johnson et al., 1984; Larsen et al., 1986; Meehan et al., 1986), ie. the scores at altitude were significantly higher than sea level scores, and the highest scores were found early in the altitude exposure, followed by progressively lower scores over time. This pattern is consistent with the gradual remission of AMS as the subjects acclimate to hypobaric hypoxia. The pattern was also present to a lesser degree when the subjects were taking dexamethasone. The decrease in scores over time was statistically significant. Additionally, some mean AMS-C scores in the 4 mg group on placebo were significantly higher than those of the other two dose groups on placebo, suggesting that the individuals in the 4 mg group were either more susceptible to AMS or more conscientious in reporting symptoms.

Dexamethasone had a significant overall effect of reducing symptom scores compared to placebo. Specifically, the 4 mg dose of dexamethasone reduced symptoms of AMS during altitude exposure, while the lesser doses did not (Table 1). The mean morning scores for AMS-C and AMS-R on 4 mg were significantly lower than placebo.

While the 4 mg dose reduced mean symptom scores on the ESQ, it did not prevent AMS from occurring in some individuals, at least not based upon previously established criterion scores for identifying "sick" individuals (AMS-C>0.7 and AMS-R>0.6; Sampson et al., 1983). Five of the eight subjects taking 4 mg dexamethasone were "sick" at some period during the altitude exposure compared to seven of eight while taking placebo. The 4 mg dose was associated with a more rapid resolution of cerebral symptoms than occured during placebo administration. Only two of the eight subjects taking 4 mg dexamethasone met the criteria for having AMS at the end of the exposure compared to seven of the eight while taking placebo.

The results of the clinical interview confirm the subjective findings from the ESQ. Although 4 mg and 1 mg doses of dexamethasone generally reduced the mean scores compared to placebo on the Johnson scale, only those for the 4 mg dose during the first test period was statistically significant (Table 1). Again, dexamethasone did not prevent AMS based upon the number of individuals judged "sick" based on the previously established criterion of a score $\geq$ 1. Six of the eight taking 4 mg dexamethasone were "sick" at some period during the altitude exposure compared to all eight on placebo. Also, again, 4 mg dexamethasone appeared to hasten recovery, for only two of the eight on that dose were sick at the end of the altitude exposure, compared to seven of the eight on placebo.

The improvement in objective appearance while on the higher doses of dexamethasone was apparent to other test subjects during the periods between symptom assessment. Peer rating mean scores in subjects taking 4 mg dexamethasone were lower than placebo during all periods at altitude and were lower in all but the final period in subjects taking 1 mg (Table 1). The difference was statistically significant at the 4 mg dose during the first, third and fourth test periods. In contrast to the results on the ESQ and the clinical interview, 4 mg dexamethasone appeared to prevent AMS in more individuals based on a criterion score of $\geq$1. Using this criterion, only three of eight individuals were judged to have AMS while taking 4 mg dexamethasone during altitude exposure, compared to seven of those eight while taking placebo.

Altitude exposure had a significant effect on the parameters of body fluid balance measured during this study, but treatment with dexamethasone did not. Fluid intake was significantly decreased from 2436.7±140.0 ml at sea level to 1587.0±129.4 ml and 1420.1±114.8 ml on days 1 and 2 of altitude exposure respectively ($p<.05$). Urine volume during these same periods fell significantly from 1640.9±129.2 ml to 1284.9±111.0 ml and 945.9±82.4 ml ($p<.001$). There were no significant changes in percent plasma volume, although Hb and Hct values increased significantly from 14.6±.2 mg/dl and 43.6±.4 % at sea level to 15.7±.2 mg/dl and 46.7±.3 % on day 2 at altitude ($p<.001$). The subjects' mean body weight decreased significantly from 80.1±2.1 kg at sea level to 78.3±2.0 kg on day 2 at altitude ($p<.001$). There were no significant differences between dexamethasone and placebo treatments or between dose levels of dexamethasone for any of these parameters.

Resting plasma cortisol levels showed significant diurnal variation with the highest values occurring in the morning samples (Table 2). This pattern was superimposed upon altitude and treatment effects. Both 1 mg and 4 mg of dexamethasone caused a significant decrease in plasma cortisol levels compared to placebo. Altitude exposure caused a significant increase in cortisol levels except during treatment with 1 mg and 4 mg of dexamethasone.

Treatment with dexamethasone did not cause any apparent adrenal suppression at 48 h post exposure. Mean cortisol levels increased from a baseline of 16.6±.6 μg/dl to 26.5±.6μ g/dl at 60 min following ACTH stimulation. There were no significant differences between placebo and control values and no differences between dose levels.

DISCUSSION

The results of this study indicate that 4 mg dexamethasone every 12 h will reduce the symptoms of AMS, whereas doses of 1 mg and 0.25 mg are ineffective. That conclusion is based upon the finding of significantly lower symptom scores in subjects taking 4 mg dexamethasone during altitude exposure compared to taking placebo during a similar exposure. The validity of these findings is strengthened by the observation that the three independent assessments of AMS used in this double-blind, crossover study each showed the same results. A possible caveat is the fact that the placebo scores for the 4 mg group were higher, and in some instances significantly so, than placebo scores for the other two groups. The explanation for that finding is not apparent. Given that the subjects were assigned to the treatment at random, that the order in which they were exposed to either dexamethasone or placebo was counter-balanced within treatment groups, and that they were exposed to altitude in mixed groups containing individuals from at least two dose levels, we would not have expected significant differences in placebo scores. The difference in placebo scores does not affect the conclusion that prophylactic use of dexamethasone reduces AMS symptoms since that conclusion is based on crossover data. The differences between dose levels is more problematic. However, the fact that the number of sick individuals based on preestablished criterion values for each symptom score was less in the 4 mg compared to the other treatment groups, further strengthens the conclusion that 4 mg was more effective than 1 mg or 0.25 mg.

The finding that dexamethasone is an effective prophylactic for AMS confirms the results of previous studies in a hypobaric chamber (Johnson et al., 1984) and on the summit of Pikes Peak, Colorado (Rock et al., in press), but, importantly, extends those observations to dose levels under 16 mg/day. No study examining the effect of lower doses has yet been reported in the literature; however, one group of investigators has looked at the effect of using 2 mg dexamethasone every 6 h in active and sedentary individuals flown to 14,000 ft on Denali in Alaska. They found that that dose was effective in preventing AMS in the sedentary group, but not in the active group (P. Hackett, personal communication). The subjects in the present study were sedentary.

It is important to note that although the 4 mg every 12 h dose (8 mg/day) was effective in reducing symptom scores, it did not appear as effective as the 4 mg every 6 h dose (16 mg/day) regimen used in earlier studies. For instance, the mean AMS-C scores in subjects on 8 mg/day dexamethasone in the present study were reduced by 52.3 % compared to a reduction of 77 % in subjects taking 16 mg/day under the same conditions in the earlier hypobaric chamber study (Johnson et al., 1984). This result was not expected, for both 8 mg and 16 mg dexamethasone per day are clearly pharmacologic doses, and both effectively suppressed cortisol secretion.

There are at least two possible explanations as to why the 8 mg/day was less effective than the 16 mg/day dose. One is that the prophylactic effect of dexamethasone follows a dose response curve and is progressively less at lower doses. The fact that the symptom scores did not increase progressively with the 2 mg/day (1 mg every 12 h) and 0.50 mg/day (0.25 mg every 12 h) dose regimens mitigates against this explanation; although it could be argued that there is a threshold between 2 mg/day and 8 mg/day, below which dexamethasone has no effect on AMS. Certainly 2 mg/day and 8 mg/day were both effective in suppressing cortisol secretion; although again it could be argued that the effect on cortisol is independent of the effect on AMS symptoms.

The other possible reason for the decreased effectiveness of the 8 mg/day dose of dexamethasone is that the timing of administration played a role. The twice a day administration used in the present study was chosen to reduce the total amount of steroid taken during a 24 h period. Because dexamethasone has a long biologic half-life it was felt that a twice daily regimen would still be effective. On the other hand, although the serum half-life of dexamethasone is long, it is well recognized clinically that it must be administered frequently (every 4-6 h) in the treatment of cerebral edema.

There is no way to distinguish between these two possible explanations of the apparent decreased effectiveness of 8 mg/day or less of dexamethasone on the basis of the data from this study. The actual explanation depends upon the mechanism of action of dexamethasone in preventing AMS, and that has not been determined. Indeed, the pathophysiologic mechanisms underlying AMS have never been convincingly demonstrated, although there is a general consensus that the symptoms are due to a hypoxia-induced subclinical cerebral edema of either vasogenic or cytotoxic origin (Sutton and Lassen, 1979; Hansen and Evans, 1970). Presumably dexamethasone prevents edema formation by preventing disruption of blood brain barrier tight junctions or increased pinocytotic activity in capillary endothelial cells (Long and Holaday, 1985). It may also reduce blood flow in cerebral microcirculation (Soejima et al., 1979) or CSF formation, both of which could reduce edema formation or decrease pressure on brain tissue by decreasing the fluid volume in the cranial cavity. Although dexamethasone has been shown to alter the overall fluid balance of the body in cerebral edema (Shenkin and Gutterman, 1969), there was no evidence for that effect in the present study.

The observation that doses of dexamethasone less than 16 mg/day are not as effective in preventing AMS symptoms has some practical implications for the use of this agent in that role. Although high doses of dexamethasone are effective in preventing AMS, our study indicates that lower doses, which would likely have a lower risk of side effects, are not particularly effective in preventing symptoms. These facts and the observation that AMS symptoms seem to develop after dexamethasone has becons eruptly discontinued (Rock et al., in press) suggest that this drug may be most successfully used in a treatment rather than a prophylactic role. There is some evidence that it may work very well for early treatment of severe AMS symptoms (Ferreira and Grundy, 1985; P. Hackett, personnel communication). That aspect of its use may be a fruitful area of investigation in the future.

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Human subjects participated in this study after giving their voluntary informed consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on the use of volunteers in research. The views, opinions and findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy or decision unless so designated by other official documentation.

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TABLE 1. SYMPTOM SCORES DURING SEA LEVEL AND ALTITUDE EXPOSURE.

DOSE	AMS-C		AMS-R		JOHNSON SCORE		PEER REVIEW	
	Placebo	Dexamethasone	Placebo	Dexamethasone	Placebo	Dexamethasone	Placebo	Dexamethasone
0.25 mg SEA LEVEL	.08±.03	.05±.02	.12±.02	.06±.02	.06±.02	.00±.00	.00±.00	.00±.00
ALT 1 AM	1.44±.41∇	1.80±.56	1.07±.28	.83±.21	1.38±.32	2.00±.38	.60±.16	.54±.16
PM	.88±.34∇	.93±.37	.64±.26	.70±.27	.50±.27	.88±.30	.44±.15	.38±.17
ALT 2 AM	.84±.47∇	.96±.37	.71±.31	.58±.20	.75±.31	1.00±.33	.35±.13	.38±.16
PM	.68±.45	.66±.41	.44±.29	.46±.20	.38±.26	.29±.25	.17±.13	.25±.16
1.0 mg SEA LEVEL	.10±.04	.05±.01	.10±.04	.09±.02	.00±.00	.06±.01	.02±.02	.00±.00
ALT 1 AM	2.02±.35	1.93±.41	1.17±.21	.88±.20*	2.78±.22	2.22±.36	.89±.12	.85±.16
PM	1.18±.30	1.14±.32	.62±.20	.55±.15	1.44±.24	1.11±.39	.80±.15	.79±.23
ALT 2 AM	.73±.14∇	.89±.22	.50±.13∇	.57±.11	.89±.11	.75±.14	.56±.14	.40±.11
PM	.53±.17∇	.73±.21	.37±.31	.35±.08	.56±.18	.75±.22	.20±.08	.28±.15
4.0 mg SEA LEVEL	.13±.03	.16±.05	.11±.03	.12±.03	.06±.02	.00±.00	.02±.02	.00±.00
ALT 1 AM	2.71±.36+	1.08±.25*	1.35±.20	.56±.08*	2.50±.38	1.38±.42*	1.19±.24	.45±.19*
PM	2.05±.37+	1.27±.45	.94±.22	.52±.15	1.63±.42	1.38±.50	.93±.28	.51±.27
ALT 2 AM	2.24±.49+#	.87±.39*	1.25±.38#	.46±.19*	2.00±.33	.57±.37	1.05±.26	.29±.20*
PM	1.45±.36#	.81±.40	.55±.14	.36±.11	1.38±.38	.57±.37	.67±.24	.24±.21*

* Different from Placebo $P<.05$
\+ Different from 0.25 mg $P<.05$
\# Different from 1.0 mg $P<.05$
∇ Different from 4.0 mg $P<.05$
AMS-C = Cerebral symptom score
AMS-R = Respiratory symptom score
ALT 1, ALT 2. = First and second day of simulated altitude exposure.

TABLE 2. PLASMA CORTISOL LEVELS (μg/dl)

DOSE	AM VALUES			PM VALUES		
	SL	DAY 1	DAY 2	SL	DAY 1	DAY 2
0.25 mg						
Placebo	15.8±1.5	20.8±3.1	17.9±1.6∇	6.7±1.2	15.6±2.4∇	12.8±1.2
Dex	13.4±1.3	20.6±3.3∇	13.8±2.7	1.6±0.2	8.4±2.9∇	6.5±2.2*
1.0 mg						
Placebo	16.6±1.9	28.4±2.6	20.9±2.5+	10.3±1.7	20.2±3.1∇	18.2±2.1
Dex	18.0±1.9∇	22.8±4.5∇	11.8±4.3*	2.0±0.5	13.0±4.1∇	6.0±3.2*
4.0 mg						
Placebo	17.6±2.0	28.8±2.4	28.4±3.7+	8.8±1.2#	21.3±3.7	20.2±3.3
Dex	13.5±1.3	5.8±3.3#+*	5.6±2.7*	2.5±0.6	2.4±0.9#+*	1.1±0.2*

* Different from Placebo P<.05
\+ Different from 0.25mg P<.05
\# Different from 1.0mg P<.05
∇ Different from 4.0mg P<.05

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